Statistical Analysis Plan Amendment	
Study Code	D5290C00008
Edition Number	3
Date	17 November 2022

A Phase 2, Open-label, Uncontrolled, Single-dose Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Occurrence of Antidrug Antibody for Nirsevimab in Immunocompromised Children ≤ 24 Months of Age

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Abbreviation or special term	Explanation
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
CBC	complete blood count
CI	confidence interval
COVID-19	coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
CSP	clinical study protocol
CSR	clinical study report
CV	coefficient of variation
DAIDS	Division of AIDS
DCO	data cut-off
eCRF	electronic case report form
ED	emergency department
FDA	Food and Drug Administration
GMC	geometric mean concentration
GMFR	geometric mean-fold rise
HRU	healthcare resource utilization
ICU	intensive care unit
IM	intramuscular
IP	investigational product
IPD	important protocol deviation
LLOQ	lower limit of quantification
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing anti-drug antibody
NOCD	new onset chronic diseases
OTC	over-the-counter
PK	pharmacokinetics
PT	preferred term

Abbreviation or special term	Explanation
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cell count
YTE	M257Y/S259T/T261E triple amino acid substitution

AMENDMENT HISTORY

Version	Date	Description of change
1.0	30 June 2020	Initial signed version
Amendment 1	21 December 2021	Key change compared to previous signed version is the expansion of the study from Japanese to a Global study. Other minor changes are listed below:
		• Editorial changes for clarification. • Section 1.2 and 1.3, updated as per protocol to increase number of sample size and study expansion. • Section 2.1, added new analysis set for Japan population only. • Section 2.2.1, added an summary for IPDs which are related to COVID-19. • Section 3.1.3, updated the analysis of skin reactions (including hypersensitivity reactions) to two separate analyses of skin reactions and skin hypersensitivity reactions. • Section 3.3.4, removed the number and type of outpatient visits. • Section 4.1, changed the number of planned analysis from one to two, an interim analysis and a final analysis. Also added a description for visit-based summaries for ADA, CCI and clinical laboratory data. Also added a description to explain that the presentation of analysis tables is to be presented by season and total. • Section 4.1.1, updated treatment group from MEDI8897 to nirsevimab. • Section 4.1.4, updated imputation rules for partial AEs dates and added imputation rule for partial concomitant medications dates. • Section 4.1.5, new section added for implementation of data cut-off at interim analysis. • Section 4.2.1, added a new summary for subjects enrolment by hemisphere, country and site. • Section 4.2.2, removed RSV season from the summary of demographic and baseline

		characteristics, and added gestational age and summary of inclusion criteria 2. • Section 4.2.4.1, added the summary of IP-related AEs, AESI based on investigator assessment, AESI based on selected MedDRA PT codes, skin reactions and skin hypersensitivity reactions. • Section 4.2.4.2, added description for AESI based on investigator assessment and AESI based on selected MedDRA PT codes. • Section 4.2.4.3, split the analysis of skin reactions (including hypersensitivity reactions) to two separate analyses of skin reactions, and skin hypersensitivity reactions. • Section 4.2.4.5, remove subgroup analysis by RSV season. And added one extra subgroup to the subgroup analysis by AE onset time relative to dosing. • Section 4.2.5.1, added description for PK analysis. • Section 0, added description for the analysis of ADA. • Section 4.2.5.3, removed the summary of incidence of MA RSV LRTI by inpatient and outpatient settings. The analysis with break down by hospitalization setting is also removed. The summary of central or local testing are presented separately. Added a new table, Table 1 to describe the analysis endpoints. • Section 284.2.6.1 and Section 4.2.6.2, added new summaries and analyses for PK and ADA. • Section 4.2.6.4, removed the summary of visiting outpatient facilities. And added a description to report HRU by the analysis endpoints described in Table 1. Also updated the analysis of OTC medication to pre-specified OTC medication (analgesics/antipyretics), pre-specified prescription medication (systemic antibacterial agents) and anti-wheezing medication. • Section 4.2.7.1, added a text to explain that clinical laboratory data will only be presented for Japan population.

		• Section 4.2.7.3, added a summary for medical history and summary for vaccination received within ±14 days of IP dosing. • Section 4.2.7.4, new section added analyses to examine impact on analyses due to COVID-19 pandemic. • Section 5.1 and Section 5.2, new sections added for interim analysis and data monitoring committee.
		• Section 2.1, updated analysis sets to 'as-treated population' and 'as-treated Japan subpopulation'. • Section 3.3.4, added 'number and type of outpatient visits' back to the HRU measures. • Sections 3.1 and 4.2.4.1, updated MedDRA version to 24.1 or higher. • Section 4.2.4.1, added IP related AESIs based on investigator assessment. • Sections 4.2.4.2 and 4.2.4.3, added new analysis by highest severity. • Section 4.2.5.1, added a new PK analysis of nirsevimab serum concentration by inclusion criterion number 2. • Section 0, added that ADA results will not be imputed and added derivations for treatment-emergent ADA negative and treatment-emergent ADA positive. • Section 4.2.6.4, added back summary of visiting outpatient facilities. • Appendix 2, updated analysis window for PK/ADA/RSV. • Appendix 4, new appendix.
		• Section 1.2, study design updated based on information provided by note-to-file memo, where recruitment is based on subjects age and weight and not RSV season. • Section 4.1, updated the presentation of data from being by subjects age at dosing to actual dose administered, 'nirsevimab 50mg/100mg' and 'nirsevimab 200mg'. • Section 4.2.5.1, added new spaghetti plots for subjects nirsevimab serum concentration over time

		by disease conditions under inclusion criterion number 2. • Section 4.2.5.2, updated analysis groups to 'nirsevimab 50mg/100mg' and 'nirsevimab 200mg'. • Section 4.2.5.3, added new analysis of MA LRTI and MA LRTI with hospitalization. • Sections 4.2.6.1 and 4.2.6.2, changed box plots to line plots. • Appendix 2, updated and added new table to clarify timepoints for PK analysis between Global and Japanese subjects.
Amendment 2	15 June 2022	• Section 4.1.5 specified the data cut-off (16May2022) and indicated that this data cut-off will be displayed in the header of the tables, listings and figures. • Section 5.1 added the name of the document with the tables, listings and figures.
Amendment 3	16 Nov 2022	• During the study conduct a need for a second interim analysis was identified and details are included in Section 5.2. • For the deviation of summary statistics for PK data, new rules are defined to be in-lines with other nirsevimab studies (CCI [redacted]) (Section 4.1).

1 STUDY DETAILS

This is the statistical analysis plan (SAP) for study D5290C00008. The SAP expands on the statistical analyses specified in the clinical study protocol (CSP). Any changes to any specifications in the CSP will be described in Section 6 of this document.

This SAP is based on the CSP Amendment Version 3.0, dated 23 June 2021 (global amendment), and 4 July 2021 (Japan amendment).

1.1 Study objectives

The study objectives are to evaluate the safety and tolerability, pharmacokinetics (PK), occurrence of anti-drug antibody (ADA) and efficacy for nirsevimab in immunocompromised children ≤ 24 months of age.

1.1.1 Primary objective

The primary objective is to evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age.

1.1.2 Secondary objectives

The secondary objectives are:

- To evaluate the PK of nirsevimab.
- To evaluate the ADA responses to nirsevimab in serum.
- To assess the efficacy of nirsevimab when administered as a single intramuscular (IM) dose to infants ≤ 24 months of age.

1.1.3 Exploratory objectives

The exploratory objectives are:

CCI [redacted]

- To assess healthcare resource utilization (HRU) for nirsevimab recipients.

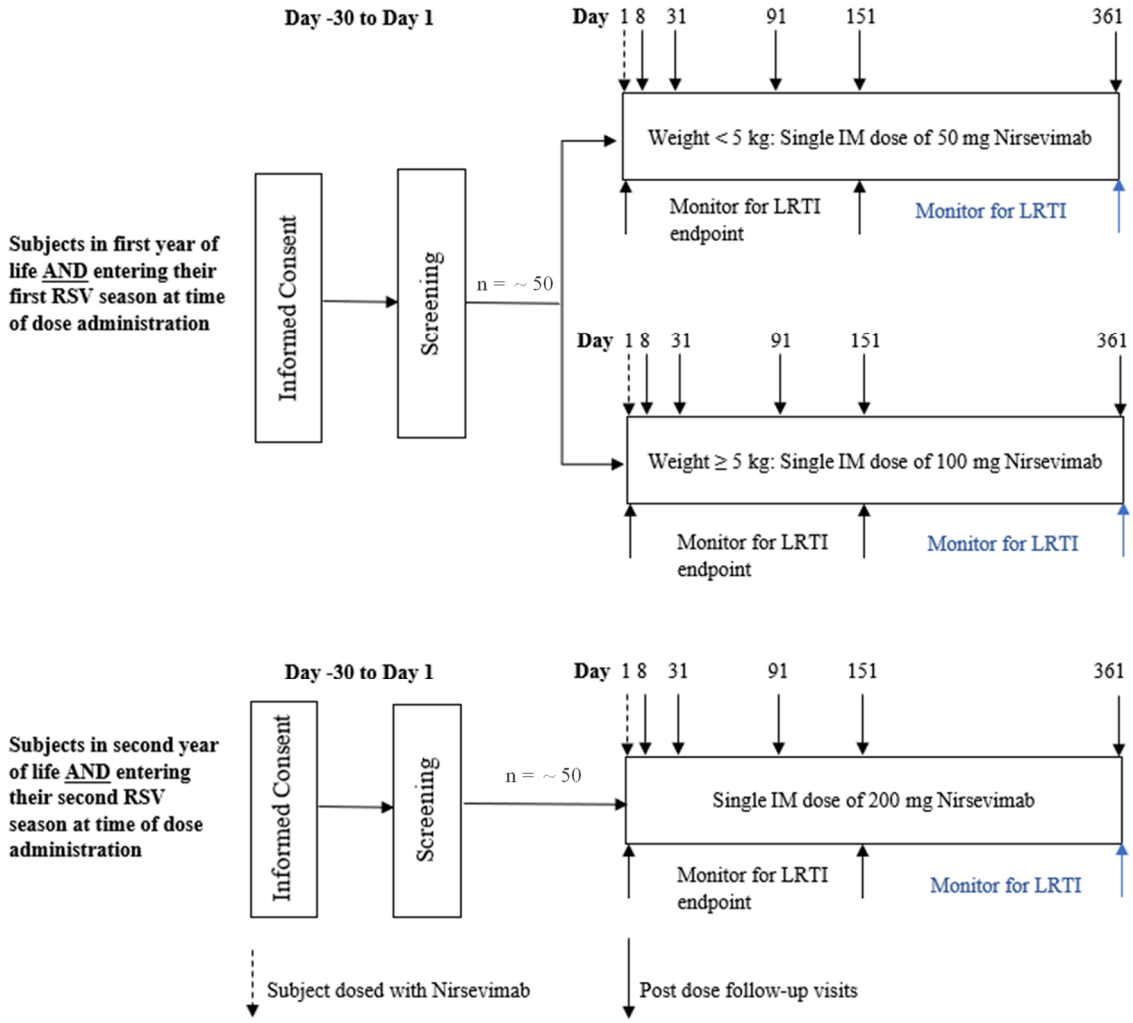
1.2 Study design

This is a Phase 2, open-label, uncontrolled single-dose study to assess the safety and tolerability, PK, occurrence of ADA, and efficacy of nirsevimab in immunocompromised children who are ≤ 24 months of age at the time of dose administration. The study is planned to be conducted in South Africa, the United States, and the European Union, in addition to Japan, where enrolment in the study originated. Approximately 100 subjects will be enrolled. Due to atypical RSV circulation and RSV seasons in 2020/2021, the RSV season will not be

considered for dose selection. The dose of nirsevimab is administered only based on the age and body weight regardless of the first or second RSV season subjects is entering. Subjects who are in their first year of life at the time of dose administration will receive nirsevimab as a single, fixed IM dose of 50 mg if body weight < 5 kg or 100 mg if body weight ≥ 5 kg. Subjects in their second year of life at the time of dose administration will receive nirsevimab as a single, fixed IM dose of 200 mg. Subjects will be followed up for approximately 1 year after dose administration.

A flow diagram of the study design is presented in Figure 1.

Figure 1 Study Flow Diagram



IM = intramuscular; LRTI = lower respiratory tract infection; n = number of subjects; RSV = respiratory syncytial virus.

1.3 Number of subjects

A total of approximately 100 subjects are planned to receive a single IM dose of nirsevimab to evaluate the safety, PK, ADA, and efficacy, which will be assessed descriptively. The original proposed sample size, as stated in the original CSP dated 27 January 2020, was based on a similarly designed palivizumab study in a similar population (Mori, et al. 2014), and it is expected to be sufficient in establishing a PK profile that allows extrapolation of efficacy and safety data from the Phase 2b (D5290C00003) and Phase 3 ([redacted]) studies in healthy preterm and term infants to the target immunocompromised population. The updated sample size of 100, from the original sample size of 30 as stated in the original CSP, allows for the collection of PK and safety data from a larger cohort of immunocompromised children, and for the study of immunocompromised children and the various causes for this condition globally. Further, the data from this study will support the evaluation of safety in a diverse population, which could potentially facilitate the examination of subpopulations.

[redacted]

Subjects will not be replaced.

2 ANALYSIS SETS

2.1 Definition of analysis set

The analysis sets defined in this study are the as-treated population and the as-treated Japan subpopulation. All analyses performed are to be conducted on these populations unless stated otherwise.

The as-treated population includes all subjects who are enrolled (once written informed consent is obtained) and received any dose of nirsevimab.

The as-treated Japan subpopulation is a subset of the as-treated population and includes only subjects who were enrolled in sites located in Japan.

2.2 Violations and deviations

Subjects who do not meet eligibility criteria but are still enrolled will be analyzed according to the analysis set described in Section 2.1. There is no intention to perform a per-protocol analysis in this study.

2.2.1 Important protocol deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Only important protocol deviations will be summarized and listed in the clinical study report (CSR). The number and percentage of subjects with at least one IPD will be summarized by the categorization of protocol deviations. The number and percentage of subjects whose IPDs are related to COVID-19 will also be provided. A list of IPDs will be reviewed and finalized by the medical advisors and statisticians prior to database lock. Full details are described in the Protocol Deviation Management Plan.

3 PRIMARY, SECONDARY AND EXPLORATORY VARIABLES

3.1 Primary variables

The following safety data will be collected: treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), skin reactions, and new onset chronic diseases (NOCDs).

Adverse events and serious adverse events (SAEs) will be collected from the time of signature of informed consent through Day 361. Adverse events of special interest and NOCDs will be collected from the time of dosing through Day 361. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1 or higher.

3.1.1 Treatment-emergent adverse events and serious treatment-emergent adverse events (TEAEs and TESAEs)

Treatment-emergent adverse events are defined as AEs whose onset occurs after receiving nirsevimab and within 360 days post dose. Adverse events with completely missing onset dates and a stop date after the start date of receiving nirsevimab (or unknown stop date) will also be considered treatment emergent. A TESAE is an TEAE which is serious.

3.1.2 Adverse events of special interest (AESIs)

An AESI is an AE of scientific and medical interest specific to the understanding of the investigational product (IP), nirsevimab and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or nonserious. Adverse events of special interest are defined as AEs of immediate (type I) hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias) following the administration of nirsevimab.

3.1.3 Skin reactions and skin hypersensitivity reactions

All skin reactions and skin reactions identified as hypersensitivity/allergic reactions and the incidence and relationship to IP will be summarized by SOC and PT. It will be done for any post-dosing skin or skin hypersensitivity reactions through Day 361 to assist in determination of the etiology of the reaction. Information will be collected regardless of event severity, duration, time of onset post dosing, or relationship to IP.

3.1.4 New onset chronic disease (NOCD)

An NOCD is a newly diagnosed medical condition that is of a chronic, ongoing nature. It is observed after receiving nirsevimab and is assessed by the Investigator as medically significant. Examples of NOCDs include, but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy).

3.2 Secondary variables

3.2.1 Pharmacokinetic (PK) variables

The PK variable is nirsevimab serum concentration.

3.2.2 Anti-drug antibodies (ADA) variable

The ADA variable is the incidence of ADA to nirsevimab in serum. The impact of ADA on PK, and the association with TEAEs and TESAEs, will be assessed, if data permit.

3.2.3 Efficacy variables

The efficacy variables are the incidence of protocol-defined medically attended lower respiratory tract infections (LRTI) (inpatient and outpatient) due to reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed RSV, also described as the medically attended RSV LRTI, and the incidence of protocol-defined hospitalizations due to RT-PCR-confirmed RSV, also described as RSV LRTI hospitalization, through 150 days post dose, after 150 days post dose, and through 360 days post dose. For subjects with multiple medically attended RSV LRTI events (inpatient or outpatient) or multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis, unless stated otherwise.

The determination of medically attended RSV LRTI will be based on objective clinical LRTI criteria (described in Section 4.3.1.1 of the CSP and in Appendix 1 of this SAP) and RSV central laboratory test results. Protocol-defined medically attended LRTI will be identified when at least one item of "Physical exam findings" and at least one item of "Clinical signs of severe disease" from 'Respiratory Illness Assessment' eCRF page are selected as 'yes'. If there are multiple assessment settings associated with the same event, then assessment data of those visits will be combined to determine whether the event meets criteria for the protocol-defined medically attended RSV LRTI.

Testing for RSV will be performed centrally using a United States Food and Drug Administration (US FDA)-cleared and Conformité Européenne or European Conformity marked in vitro diagnostic real-time RT-PCR assay. The RSV test results obtained from analyzing the respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A or RSV B are performed in a central laboratory. Respiratory syncytial virus tests are also performed by local laboratories, if available, and the test results are captured in the 'Respiratory Illness Assessment' eCRF page.

The events of "RSV LRTI hospitalization" are a subset of "medically attended RSV LRTI," which are determined based on objective clinical LRTI criteria (described in Section 4.3.1.1 of the CSP and in Appendix 1 of this SAP) and RSV test results obtained from central laboratory using a validated RSV RT-PCR assay for the detection of RSV A or RSV B. If any of the settings associated with the medically attended RSV LRTI is hospitalization, then this medically attended RSV LRTI will be counted as RSV LRTI hospitalization.

3.3 Exploratory variables

CCI

[redacted]

3.3.4 Healthcare resource utilization (HRU)

The magnitude of HRU will be measured by:

- the number of admissions to hospitals and duration of stay;
- the number of admissions to the intensive care units (ICUs) and duration of stay;
- the number of subjects who require respiratory support (using Continuous Positive Airway Pressure [CPAP] or mechanical ventilation) and duration of use, and the number of subjects requiring supplemental oxygen and duration of use;
- number and type of outpatient visits, eg, outpatient emergency department (ED), urgent care, outpatient clinic;
- the number of pre-specified over-the-counter (OTC) medications (analgesics/antipyretics) use;
- the number of pre-specified prescription medication (systemic antibacterial agents) use;

- the number of anti-wheezing medication use.

4 ANALYSIS METHODS

All analyses described will be conducted on the as-treated population and as-treated Japan subpopulation as defined in Section 2.1 unless stated otherwise.

No formal statistical comparisons are planned.

4.1 General principles

There are 2 planned analyses for this study: an interim analysis and a final analysis. The interim analysis will be conducted when subjects enrolled globally by the end of 2021 have been followed through Day 151. The final analysis will be conducted when all subjects have completed the last visit of the study (Day 361). The data will be validated as defined in the Data Management Plan.

- For the visit-based summaries for PK/ADA, CCI and clinical laboratory data, the summaries will be based on the scheduled visits using adjusted analysis-defined visit windows. The adjusted analysis-defined windows will be based on the collection schedule listed in the CSP and summaries will be windowed to the closest scheduled visit for those data. Visit windows have been constructed so that every observation collected can be allocated to a particular visit. All data will be included in the listings. If multiple readings are recorded within a single analysis-defined visit window, the following rules will apply: If there are 2 or more valid, non-missing observations within the same visit window, and
  - if they are on different days, then the non-missing one which is closest to the scheduled visit day will be used in the analysis.
  - if they are on the same day which is closest to the scheduled visit day, then the non-missing one with the later collection time will be used in the analysis.
- If 2 or more valid observations are equidistant from the scheduled visit, and
  - if they are on different days, then the non-missing post-dose observation with the earlier collection date will be used in the analysis for the post-baseline observations, and the non-missing pre-dose observation with the later collection date will be used in the analysis for the screening observations.
  - if they are on the same day, then the non-missing observation with the later collection time will be used in the analysis.
- For LRTI visits or unscheduled visits, if 2 or more valid observations are collected on the same day, then the non-missing observation with the later collection time will be included in the analysis.
- If a visit window does not contain any observations, then the data will remain missing.
- For the visit-based summaries for ADA, if both ADA positive and negative samples are available within a subject's visit, ADA positive will be reported.

- For summary Statistics of PK data following rules apply:
  - Handling of samples below LLOQ, samples should be imputed to the LLOQ (0.5 µg/mL)
  - Summary statistics should not be presented in case of >=50% of samples <LLOQ (see specific details of reporting in Section 4.1.7)

For assignment of data to adjusted analysis-defined visit windows, study day will be defined as defined in Section 4.1.3.

The adjusted analysis-defined windows for PK/ADA, CCI [redacted] are defined in Appendix 2, and for clinical laboratory data are defined in Appendix 3.

Data will be summarized for the overall study population, as well as for Japan only. Data will also be presented by the actual dose administered; 'nirsevimab 50mg/100mg', 'nirsevimab 200mg' and 'total', unless stated otherwise.

Data analyses will be performed by IQVIA under the direction of AstraZeneca using the SAS® System Version 9.4 or higher (SAS Institute Inc., Cary, NC) in a SAS GRID environment.

4.1.1 General data reporting conventions

Categorical data will be summarized by the number and percentage of subjects in each category. Percentages will be rounded to 1 decimal place. Continuous variables will be summarized by mean, median, standard deviation (SD), minimum, and maximum, unless stated otherwise. The mean and median will be presented with one more decimal place than the raw data. The standard deviation will be presented with two more decimal places than the raw data. Minimum and maximum values will have the same number of decimal places as the raw data.

Data collected at unscheduled visits will not be included in summaries by timepoint or visit unless stated otherwise. Data collected at unscheduled visits will be presented in listings.

In tables and listings, treatment group will be presented as 'nirsevimab'.

4.1.2 Definition of baseline

Baseline will be defined as the last non-missing value prior to administration of nirsevimab, unless stated otherwise.

4.1.3 Derivation of study day

Study day will be calculated as follows:

- If the evaluation date is on or after the administration date of nirsevimab:

study day = date of evaluation – administration date of nirsevimab + 1

- If the evaluation date is before the administration date of nirsevimab:
  study day = date of evaluation – administration date of nirsevimab

4.1.4 Handling of missing data

No imputation for missing data will be applied except for the partial dates.

4.1.4.1 General imputation rule for partial dates

- Partial dates where only the year is known:
  - For start dates assume January 1st;
  - For stop dates assume December 31st.
- Partial dates where only the month and year are known:
  - For start dates assume the first of the month;
  - For stop dates assume the end of the month.

4.1.4.2 Imputation rule for partial AE start date

- When AE range is available:

Step 1: For partial AE start dates, regardless if only the year is known, or only the month and year are known, first use the following rule to impute AE start date:

a. Assume (dose date + 1 day) if AE started ≤ 7 days after dosing;
b. Assume (dose date + 7 days) if AE started 8 - 14 days after dosing;
c. Assume (dose date + 14 days) if AE started >14 days after dosing.

Step 2: After getting an imputed AE start date from Step 1, compare the imputed AE start date with the partial AE start date:

- If partial AE start date where only the year is known:
  - If the year of partial AE start date is the same as imputed AE start date from Step 1, then use imputed AE start date from Step 1;
  - If the year of partial AE start date is different from the year of imputed AE start date from Step 1, assume partial AE start date as January 1st;
  - If the imputed AE start date is after AE end date, then set AE start date the same as AE end date.
- If partial AE start date where only the year and month are known:
  - If the year and month of partial AE start date are the same as imputed AE start date from Step 1, then use imputed AE start date from Step 1;
  - Otherwise, assume partial AE start date as the first day of the month.
  - If the imputed AE start date is after AE end date, then set AE start date the same as AE end date.

- When AE range is not available:
  - If partial AE start date where only the year is known,
    - If the same year as dosing date:

i. If AE does not occur on the same day of dosing, then AE start date is one day after dosing date;
ii. Otherwise, AE start date is the same as dosing date.

- If different year from dosing date, assume January 1st.

- If partial AE start date where only the year and month are known,
  - If the same year and month as dosing date:
    i. If AE does not occur on the same day of dosing, then AE start date is one day after dosing date;
    ii. Otherwise, AE start date is the same as dosing date.
  - Otherwise, assume the first day of that month.

4.1.4.3 Imputation rule for partial concomitant medications dates

- If a concomitant medication is not associated with an AE:
  a. Apply general imputation rule described in Section 4.1.4.1 wherever it fits.
- If a concomitant medication is associated with an AE:
  a. The concomitant medication start date will be imputed with either observed or imputed AE start date described in Section 4.1.4.2. If there are multiple associated AEs, the earliest AE start date either observed or imputed will be used for imputation.
  b. The concomitant medication end date will be imputed by the general imputation rule described in Section 4.1.4.1 for end date whenever fits. Then compare the imputed concomitant medication start date or end date with the data cut-off and apply the implementation rule for data cut-off for interim analysis described in Section 4.1.5. If the imputed concomitant medication end date is after the end of study date, then the concomitant medication end date will be replaced with the end of study date.

4.1.5 Implementation of data cut-off (DCO) for interim analysis

The principle is to only report the data collected up to the DCO date (16May2022) for the interim analysis.

- Partial dates will be imputed before applying DCO.
- Records with start date after DCO will be removed in SDTM datasets
- If end date is after DCO, then end date will be reset as missing, event status will be reset as ongoing in SDTM datasets if applicable.

The date of DCO is displayed in the header of tables, listings and figures for DCO applied outputs as: ‘Interim Analysis: Data cut-off = 16MAY2022’. If outputs are produced before IA a prefix is added as ‘Pre-‘.

4.1.6 Character values of clinical laboratory variables

Quantitative laboratory measurements reported as “< X” or “≤ X”, ie, below the lower limit of quantification, or “> X” or “≥ X”, ie, above the upper limit of quantification, will be converted

to half of X or X for the purpose of quantitative summaries, but will be presented as recorded, ie, as "< X" or "> X" in the listings.

For ADA titer reported as "< X" or "≤ X", refer to Section 0 for details.

4.1.7 Reporting PK concentration

Individual compound concentrations below the lower limit of Quantification (LLOQ) of the assay are reported as NQ (not quantifiable) with the LLOQ defined in the Tables, Figures and Listings (TFLs).

For descriptive statistics:

- If, at a given time point, 50% or less of the plasma concentrations are not quantifiable (NQ), the geomean, coefficient of variation (CV), geoSD, arithmetic mean and standard deviation (SD) are calculated by substituting the limit of quantification (LOQ) for values which are NQ.

- If more than 50%, but not all, of the concentrations are NQ, the geomean, CV, geoSD, arithmetic mean, and SD are reported as not calculable (NC). The max value is reported from the individual data, and the min and median are set to NQ.

- If all the concentrations are NQ, the geomean and arithmetic mean are reported as NQ and the CV, geoSD and SD as NC.

- The number of values below LLOQ are reported for each time point along with the total number of collected values.

Three observations >LLOQ are required as a minimum for a plasma concentration to be summarized. Two values are presented as a minimum and maximum with the other summary statistics as NC.

For consistency, the same plasma concentration values are used in the mean data graphs as those given in the descriptive statistics summary table for each time point.

4.2 Analysis methods

4.2.1 Subject disposition and completion status

A summary of subject eligibility, reasons for screen failure, reasons for early discontinuation and enrolment status as well as treatment received (including summary of subjects enrolled but not dosed) will be provided. In addition, disposition of subjects throughout the study, number of subjects who completed Day 151 for inclusion in the efficacy evaluation and number of subjects who completed the study (Day 361) as planned, will be provided. The

denominators for this summary will include all subjects who were enrolled and dosed unless stated otherwise. In addition, subjects who discontinued the study will also be listed.

Subjects enrolment will be presented by hemisphere, country, and site, with the date of first and last subjects IP administration, and the date last subject evaluated. This will be presented for the as-treated population only.

The number of subjects in the as-treated population and the as-treated Japan subpopulation will be provided.

4.2.2 Demographic and baseline characteristics

A summary of demographic information related to sex, ethnicity, race, age at IP administration (months) calculated from eCRF, age category at IP administration calculated from eCRF (age < 12 months, age ≥ 12 months), birth weight (kg), birth weight category (weight ≤ 2.5 kg, weight > 2.5 kg), gestational age (weeks), multiple birth (yes/no), siblings enrolled in the study (yes/no), ever breastfed (yes/no), currently breastfed (yes/no), smokers in the household currently (yes/no), currently in day care (yes/no), weight (kg) on Day 1, weight category on Day 1 (weight < 5 kg, weight ≥ 5 kg to < 10 kg, weight ≥ 10 kg), subjects who met the subcategories of inclusion criteria 2 will be provided. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing.

In addition, a summary of family history of atopy (including asthma, hay fever, eczema, wheezing) will be provided.

4.2.3 Study drug exposure and treatment compliance

Due to the simplicity of dosing for this study, exposure is summarized in the Subject Disposition table under “Subjects enrolled and dosed”.

Treatment compliance will be presented by the number and percentage of subjects who have received a full dose of nirsevimab. For subjects who did not receive a full dose of nirsevimab, the number and percentage of subjects who received > 50% of full dose, 50% of full dose and < 50% of full dose will also be provided.

4.2.4 Primary analyses

Treatment-emergent AEs, TESAEs, AESIs, skin reactions, and NOCDs will be summarized using descriptive statistics.

No safety data will be imputed. The handling of partial dates for AEs is described in Section 4.1.4.2.

4.2.4.1 Treatment-emergent adverse events and treatment-emergent serious adverse events (TEAEs and TESAEs)

Adverse events will be coded by MedDRA, Version 24.1 or higher.

The number and percentage of subjects with TEAEs in any category; TESAEs in any category; IP related TEAEs; IP related TESAEs; TEAEs with ≥ grade 3 severity; TESAEs with ≥ grade 3 severity; IP related TEAEs with ≥ grade 3 severity; IP related TESAEs with ≥ grade 3 severity; TEAEs with outcome of death; AESIs based on investigator assessment; IP related AESIs based on investigator assessment; AESI based on selected MedDRA PT codes; IP related AESIs based on selected MedDRA PT codes; NOCDs; IP related NOCDs; skin reactions; and IP related skin reactions; skin hypersensitivity reactions; and IP related skin hypersensitivity reactions will be provided. In the count of subjects with TEAEs, subjects with multiple events in the same category will be counted only once in that category. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported.

Adverse events with outcome of death can be identified in the 'Adverse Events' eCRF page, when "Outcome of AE" is flagged as 'Fatal'. Other parameters such as "Serious", "AE toxicity grade", "Relationship, investigational product", "Adverse event of special interest" (based on investigator assessment), "NOCD", and "Skin reaction" can also be identified in the same 'Adverse Events' eCRF page.

All TEAEs and TESAEs will be provided by the number and percentage of subjects with the categorization by MedDRA system organ class (SOC) and preferred term (PT), the total number of TEAEs and TESAEs will also be provided. Key information such as subject identifier, sex, age, country, TEAE with SOC and PT, start and stop date of TEAE , duration of TEAE, TESAE and type of TESAE, outcome of TEAE, action taken with nirsevimab and causality to nirsevimab, will be listed for subjects with TEAEs.

The number and percentage of subjects with TEAEs, as well as categorization by MedDRA SOC and PT, and the highest severity will be provided.

The number and percentage of subjects with IP related TEAEs and TESAEs, as well as categorization by MedDRA SOC and PT will be provided.

The number and percentage of subjects with TEAEs with outcome of death, as well as categorization by MedDRA SOC and PT will be provided. Key information similar to those mentioned above will be listed for subjects with outcome of death.

Non-treatment-emergent AEs/ SAEs, defined as AEs/SAEs that occur prior to administration of nirsevimab or after Day 361, will be presented in an AE listing.

4.2.4.2 Adverse events of special interest (AESIs)

Investigators have been requested to identify the AESIs in reporting. The primary interpretation of data will be made upon those events with investigator assessment. In addition, a supplementary analysis is conducted which runs the narrow Standardised MedDRA Queries (SMQs) for hypersensitivity, the narrow and broad SMQS for anaphylactic reactions, and a study specific query based on compatible PTs for thrombocytopenia and immune complex disease occurring in the database. Narrow hypersensitivity SMQs include some PTs of immune complex disease. These SMQs and PTs will be provided by the medical monitor in a separate document before DBL of each analysis.

See Section 3.1.2 for definition of AESIs.

The number and percentage of subjects with treatment-emergent AESIs, as well as categorization by MedDRA SOC and PT and the total number of AESIs will be provided.

The number and percentage of subjects with treatment-emergent AESIs, as well as categorization by MedDRA SOC and PT, and the highest severity will also be provided.

Key information similar to those mentioned in the TEAE section will be listed for subjects with AESIs.

4.2.4.3 Skin reactions and skin hypersensitivity reactions

The incidence of treatment-emergent skin reactions, skin hypersensitivity reactions and the relationship to IP will be summarized by MedDRA SOC and PT, and the total number of skin reactions and skin hypersensitivity reactions will also be provided. A listing of subjects with skin reactions will also be provided.

The number and percentage of subjects with treatment-emergent skin reactions, as well as categorization by MedDRA SOC and PT, and the highest severity will also be provided.

The number and percentage of subjects with a hypersensitivity/allergic reaction, skin reaction etiology, types of skin reaction, skin reaction distribution, location of skin reaction, history of recent viral illness, the accompanied systemic symptoms and types of drugs exposure to within 14 days of the onset of skin reaction symptoms, as reported on the dedicated eCRF page, will be provided.

4.2.4.4 New onset chronic diseases (NOCDs)

New onset chronic diseases will be assessed and identified by the Investigator and recorded in the eCRF. The analysis of NOCD will be performed on AEs which have ‘yes’ selected for “NOCD” in the ‘Adverse Events’ eCRF page.

The number and percentage of subjects that are defined as NOCD, as well as categorization by MedDRA SOC and PT, and the total number of NOCD will be provided. Key information similar to those mentioned in the TEAE section will be listed for subjects with TEAEs that are defined as NOCDs.

4.2.4.5 Subgroup analyses

The following subgroup analysis will be performed on the primary analyses.

Subgroups by AE onset time relative to dosing

All AE start dates relative to administration date of nirsevimab will be calculated according to study day defined in Section 4.1.3. The categories for this subgroup are:

- 'within 1 day' of administration of nirsevimab; defined as study day ≤ 1.
- 'within 3 days' of administration of nirsevimab; defined as study day ≤ 3.
- 'within 7 days' of administration of nirsevimab; defined as study day ≤ 7.
- 'within 14 days' of administration of nirsevimab; defined as study day ≤ 14.

The primary analyses described in the above sections will be repeated for this subgroup analysis.

4.2.5 Secondary analyses

4.2.5.1 Pharmacokinetics

Nirsevimab serum concentration data for each nominal sampling time will be summarized by dose using descriptive statistics, including n < lower limit of quantification (LLOQ), geometric mean, geometric coefficient of variation (CV) (%), geometric SD, geometric mean +/- geometric SD, and the summary statistics listed in Section 4.1.1, and a listing of nirsevimab serum concentrations will also be provided. Line plot of geometric mean of nirsevimab serum concentration on log-normal scale will be plotted by scheduled visit. Geometric mean and other summary statistics are derived from planned visit day +/- 14 days.

Nirsevimab serum concentration at each scheduled visit will be summarized by subject disease conditions as defined in inclusion criterion number 2, see Appendix 4. The summary statistics of number of subjects, mean, SD, minimum and maximum will be provided. A series of spaghetti plots, will be created for each of the disease conditions stated in inclusion criterion number 2, presenting individual subjects nirsevimab serum concentration over time.

Individual nirsevimab serum concentrations with geometric mean +/- geometric SD will be graphically illustrated, and summarized, by ADA status (ADA positive and ADA negative). Definitions of ADA status are described in Section 0.

4.2.5.2 Anti-drug antibody (ADA)

Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in the CSP. ADA result from each sample will be reported as either positive or negative; samples without an ADA result will not be imputed. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of neutralizing anti-drug antibody (nAb) and anti-YTE will be tested for all ADA-positive samples using validated ligand-binding assays. The nAb and anti-YTE results will be reported as positive or negative.

The number of subjects in the as-treated population and the as-treated Japan subpopulation (defined in Section 2.1) who fulfil the following the criteria will be determined. The percentage of ADA-positive subjects in each of the categories specified below will be calculated, using the number of subjects with any ADA result at baseline and/or post-baseline during the study as the denominator. A subject is defined as being ADA positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise ADA negative. Missing ADA result will not be imputed.

- ADA positive at any visit; the percentage of ADA-positive subjects is known as ADA prevalence.
- Treatment-emergent ADA defined as the sum of both treatment-induced and treatment-boosted ADA; the percentage of subjects fulfilling this criterion is known as ADA incidence.
- ADA positive at both post-baseline and baseline.
- ADA positive post-baseline and not detected at baseline (treatment-induced ADA).
- ADA not detected post-baseline and positive at baseline.
- Treatment-emergent ADA-negative, defined as ADA-positive at any visit but not fulfilling the definition of treatment-emergent ADA-positive.
- Treatment-emergent ADA positive with maximum titer higher than median of maximum titers. The median of maximum titers is calculated based on the maximum titer for each ADA-positive subject within the actual dose administered group; ‘nirsevimab 50mg/100mg’ and ‘nirsevimab 200mg’ (including both baseline and post-baseline measurements).
- Treatment-boosted ADA, defined as a baseline positive ADA titer that was boosted to a 4-fold or higher level (greater than the analytical variance of the assay) following drug administration.
- Persistently positive ADA, defined as negative at baseline and having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement or an ADA positive result at the last available assessment.
- Transiently positive ADA, defined as negative as baseline and having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- nAb positive at any visit (nAb prevalence).

  - nAb positive post-baseline only (nAb incidence)
- anti-YTE positive at any visit (anti-YTE prevalence).
  - anti-YTE positive post-baseline only (anti-YTE incidence)

To evaluate the impact of ADA on safety, TEAE and TESAE by MedDRA SOC and PT will be summarized by ADA post-baseline status (ie, at least one post-baseline ADA positive or not through 360 days post dose).

Samples with ADA titer < 50 will be regarded as negative results and samples with ADA titer ≤ 50 (borderline positive) will be regarded as positive results. The evaluation on the impact of ADA on PK is described in Section 4.2.5.1.

4.2.5.3 Efficacy analyses

The analyses of the efficacy endpoints, including the incidence of protocol-defined medically attended RSV LRTI (also described as the medically attended RSV LRTI) through 150 days post dose, as well as the incidence of protocol-defined RSV hospitalization (also described as the RSV LRTI hospitalization) through 150 days post dose. The incidence will be calculated as the proportion of subjects who meet the endpoint during the reporting period. Only summaries will be provided for the efficacy analyses unless stated otherwise. The summaries will be based on observed events.

Analysis of incidence of medically attended LRTI due to RT-PCR-confirmed RSV

An analysis window which captures all relevant respiratory samples that linked to respiratory illness events will be defined prior to database lock and the decision made will be documented. In addition, deaths that can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as medically attended RSV LRTI events.

The incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose will be summarized, and a listing of subjects with medically attended RSV LRTI will also be provided. For subjects with multiple medically attended RSV LRTI events, only the first occurrence will be used in the summary.

In addition, the incidence of medically attended RSV LRTI that occurred after 150 days post dose, and through 360 days post dose will be summarized.

The incidence of medically attended RSV LRTI by subtype (RSV A or RSV B) through 150 days post dose, after 150 days post dose, and through 360 days post dose will be summarized.

Analysis of Incidence of RSV hospitalization

The events of "RSV hospitalization" are a subset of "medically attended RSV LRTI," and RSV test results are obtained from central laboratory. In addition, deaths that can be

demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as medically attended RSV hospitalization events.

The incidence of RSV hospitalization through 150 days after dosing will be summarized. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis. RSV LRTI hospitalization will also be summarized by RSV subtype (RSV A or RSV B). This summary will be based on observed events and data summary will be presented through 150 days post dose, after 150 days post dose and through 360 days post dose.

Other efficacy analyses

An overall summary of subjects with any medically attended LRTI (protocol-defined or non-protocol-defined) or hospitalization due to any respiratory illness will be presented, and a listing capturing all relevant information will also be provided. The mapping between the AE terms and LRTI or non-LRTI will be finalized before the database lock. In this summary, a subject is reported only once even though he or she might have multiple events in the reporting period. In that occasion, the event with the highest severity level will be reported. The rules to define severity among multiple LRTI events for a subject are as follows: protocol-defined > non-protocol-defined, RSV > non-RSV, and hospitalization > outpatient. The rules to define severity among multiple hospitalizations due to any respiratory illness are as follows: LRTI > non-LRTI, RSV > non-RSV. Incidence of all medically attended LRTI will be summarized by protocol-defined LRTI (RSV or non-RSV) and non-protocol-defined LRTI (RSV or non-RSV) with each further broken down by hospitalization or outpatient status.

A listing will be presented for each of the elements used to evaluate for the case definition of any medically attended LRTI (see Appendix 1 of this SAP). These elements include the following: rhonchi, rales, crackles, wheeze, increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions, grunting, dehydration due to respiratory distress. In this summary, a subject is reported once even though he or she might have the element multiple times during the reporting period.

For all medically attended LRTI events, RSV status (positive, negative or not done) will be summarized by central RT-PCR or local testing results. The proportion of each category will be calculated based on the total number of LRTI events.

Apart from the medically attended RSV LRTI and medically attended RSV LRTI with hospitalization efficacy endpoints (listed as first two endpoints in Table 1), additional four endpoints are also added to conduct similar analyses as mentioned above for exploratory purposes.

Table 1 Population for medically attend RSV respiratory illness

Type of Endpoint	Endpoint	Protocol definition of LRTI	RSV test result	Investigators assessment of LRTI/URTI	Setting of care
Secondary Efficacy	MA RSV LRTI	Protocol defined	Positive (central RT-PCR)	LRTI	Inpatient or outpatient
Secondary Efficacy	MA RSV LRTI with hospitalization	Protocol defined	Positive (central RT-PCR)	LRTI	Inpatient
CCI [redacted]					

All above stated summaries will be based on observed events and data summary will be presented through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Adverse events associated with all medically attended RSV LRTI will be summarized, as well as categorized by the MedDRA SOC and PT. Summaries will be presented through 150 days post dose, after 150 days post dose, and through 360 days post dose.

To evaluate the impact of ADA on efficacy, MA LRTI and MA LRTI with hospitalization will be summarized by ADA post-baseline status (ie, at least one post-baseline ADA positive or not through 360 days post dose).

4.2.6 Exploratory analyses

CCI [redacted]

4.2.6.4 Healthcare resource utilization (HRU)

Healthcare resource utilization will be measured as follows:

- Admissions to hospitals and duration of stay.
- Admissions to ICU and duration of stay.
- Requiring respiratory support (using initial/increased CPAP or initial/increased mechanical ventilation) and the duration of use.
- Uses and the duration of use of initial/increased supplemental oxygen.
- Visits to out-patient facilities (urgent care, outpatient ED, outpatient clinic).
- Prescription and OTC medications and duration of use.

These data will be provided through 360 days post dose and will be reported through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Specifically, to report HRU, the following summaries will be repeated for the six endpoints described in Table 1.

- The number and percent of subjects who have had at least one of the following: hospitalization, ICU admission, requiring respiratory support, requiring supplemental oxygen, or visiting an outpatient facility. Similar summaries will be provided by respiratory support subtype (initial/increased CPAP or initial/increased mechanical ventilation) and the type of outpatient facility. The percentage will be calculated for time interval through 150 days post dose, after 150 days post dose, and through 360 days post dose.
- For each of the medical activities listed above, the total number of the activity for a subject who has had at least one respective event in the reporting time-period will be calculated and summarized.
- The total duration of each of the following (in days) will be calculated cumulatively through 360 days post dose and summarized: hospital stay, ICU stay, use of respiratory support, or use of supplemental oxygen for the subjects who has had at least one of the corresponding activities.

The duration of each hospitalization will be calculated from the admission or deterioration date to discharge date. If the discharge date is missing because the subject died in the hospital, the duration of that hospital stay will be calculated from admission to the death date, or end-of-study date, whichever is the earliest. Total duration of hospitalization is the cumulated days of each hospital stay throughout the reporting time-period.

Similarly, the duration of each ICU admission, use of respiratory support, or use of supplemental oxygen will be calculated from start date to stop date, and the total duration of each medical intervention for a subject is calculated by summing the duration of all occurrences in the time interval of interest. If the use of medical intervention occurred multiple times on the same day, the duration of uses in the same day will be counted only once.

In addition, the number of pre-specified OTC medication (analgesics/antipyretics) uses; the number of pre-specified prescription medication (systemic antibacterial agents) uses; and the number of anti-wheezing medication uses will be summarized through 150 days post dose, except for the analgesics/antipyretics uses, which will be summarized through one week after dosing. The Anatomical Therapeutic Chemical Classification System (ATC) codes for these medications will be provided in a separate file by the medical monitor prior to the database lock for the Interim Analysis.

The number and percentage of subjects with pre-specified OTC medications (analgesics/antipyretics) uses within one week after dosing will be provided. The number of uses per subject (for those with the medication use) will be summarized using descriptive statistics. The same summaries will be repeated for subjects with any co-administered routine childhood vaccination (ATC code: J07) within one week of dosing.

The number and percentage of subjects with pre-specified prescription medications (systemic antibacterial agents) uses through 150 days post dose will be provided. The number of uses

per subject (for those with the medication use) will be summarized through 150 days post dose using descriptive statistics.

The number and percentage of subjects with anti-wheezing medications uses through 150 days post dose will be provided. The number of uses per subject (for those with the medication use) will be summarized through 150 days post dose using descriptive statistics.

4.2.7 Other analyses

4.2.7.1 Clinical laboratory parameters

Blood samples for determination of serum chemistry and hematology parameters will be taken at times detailed in the CSP. Clinical laboratory data will not be collected outside of Japan. Summaries of clinical laboratory parameters will be presented for as-treated Japan subpopulation only.

A summary of laboratory parameters at each visit will be provided. Frequencies of worst observed Grade 3-4 toxicity, as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [DAIDS RSC Regulatory Support Center 2017] will be presented for each laboratory parameter listed below:

- Complete blood count (CBC): hemoglobin, hematocrit, red blood cell count, platelet count.
- White blood cell count (WBC) with differential: white blood cell count.
- Liver function: total bilirubin, aspartate aminotransferase (AST)/alanine aminotransferase (ALT).
- Chemistry (general): creatinine, blood urea nitrogen.

Also, laboratory parameters will be assessed by presenting tables containing information associated with Grade 2 (or greater) laboratory shifts from baseline. All other serum chemistry and hematology parameters not listed above will be presented in the listings.

For laboratory values reported as lower than the LLOQ, a value equal to half of the limit of quantification will be imputed in the summaries. However, < LLOQ will be reported in the listings.

4.2.7.2 Potential Hy's Law and Hy's Law

A listing of subjects with TESAEs reported as Potential Hy's Law under the serious criteria of 'Important medical event' with key information such as subject identifier, sex, age, ALT, ALT × upper limit of normal (ULN), AST, AST × ULN, Total Bilirubin, Total Bilirubin × ULN at each visit will be provided.

4.2.7.3 Other safety analyses

Additional data collected throughout the study include screen failure characteristics, significant findings in medical history, vital signs, overdose report, vaccines and concomitant

medications. Data listings will be provided for these data. A listing of subjects who have taken palivizumab through 360 days post dose will also be provided.

Medical history findings and those that are ongoing at the time of signed informed consent will be summarized by SOC and PT.

In addition, the total number of vaccine doses received within ±14 days of IP dosing, will be summarized for each vaccine group. The number of subjects with co-administered vaccine doses within ±14 days of IP dosing will be summarized. The percentage will be calculated using subjects who received co-administered vaccine doses within ±14 days of IP dosing as the denominator. The ATC codes for these vaccines will be provided in a separate file by the medical monitor prior to each DBL.

4.2.7.4 Impact on analyses due to COVID-19 pandemic

The Coronavirus disease 2019 (COVID-19) pandemic has posted challenges in study conduction (including performing scheduled visit, and sample collection etc.)

Efforts are ongoing to collect outstanding data via alternative means where possible, when on-site visits cannot be performed. The following summaries have been added to assess the impact of the pandemic.

- Protocol deviations, including sample collections or visits missed due to COVID-19 related protocol deviations will be described separately in the CSR. These deviations will be identifiable in the database with a 'COVID' prefix.
- Confirmed or suspected cases of COVID-19 will be summarized and included as AEs as appropriate.
- The number of scheduled visit impacted due to COVID-19 pandemic and number of subjects with visit impacted due to COVID-19 pandemic.

5 OTHER ANALYSES

5.1 Interim analysis

An interim analysis will be conducted when subjects enrolled globally by end of 2021 have been followed through Day 151. For the interim analysis, all safety, PK, ADA, and efficacy data collected for subjects enrolled globally in 2021 will be analyzed. A minimum of approximately of 30 subjects is expected to be sufficient in establishing a PK profile for efficacy and safety extrapolation at the time of the interim analysis.

The specifications of the tables, figures and listings for the interim analysis are included in the document named 'CCI [redacted]'.

5.2 Second Interim Analysis

A new interim analysis will be conducted when subjects enrolled globally have been followed through Day 151. This lock has not been pre-planned in original protocol or amendment and it is documented though this amendment to SAP number 3. The interim analyses TFLs that will be produced are the same as those detailed in Section 5.1 except that it will include all patients globally recruited and followed up through to Day 151.

The specifications of the tables, figures and listings for the interim analysis are included in the document named "CCI [redacted]

5.3 Data monitoring committee

An independent data monitoring committee will review the safety data regularly and make recommendations regarding further study conduct.

6 CHANGES OF ANALYSIS FROM PROTOCOL

An unplanned interim analysis will be performed as detailed in Section 5.2.

For the deviation of summary statistics for PK data, new rules are defined to be in-lines with other nirsevimab studies (CCI [redacted]) (Section 4.1).

7 REFERENCES

2017. *DAIDS RSC Regulatory Support Center.* July. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Mori, M, M Onodera, A Morimoto, Y Kosaka, T Morio, and GF Notario. 2014. "Palivizumab use in Japanese infants and children with immunocompromised conditions." *Pediatric Infectious Disease Journal* 33(11):1183-5.

8 APPENDIX

Appendix 1 Criteria for Meeting the Protocol-defined Endpoint of Medically Attended RSV LRTI

RSV	Lower Respiratory Tract	Medical Significance
RSV Confirmed: • Positive by central laboratory RT-PCR assay	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration due to respiratory distress

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.

Note: One item from each column is required to meet the protocol-defined endpoint of RSV LRTI.

Appendix 2 Analysis Window for PK/ADA/CCI [redacted]

Analysis window for PK assessment:

Protocol	Scheduled Study Day	Analysis Windows
Global	Day 1	≤1
Global	Day 31	2 - 91
Global	Day 151	92 - 255
Global	Day 361	≥ 256
Japan	Day 1	≤1
Japan	Day 8	2 – 20
Japan	Day 31	21 - 91
Japan	Day 151	92 - 255
Japan	Day 361	≥ 256

Analysis window for ADA/CCI [redacted]

Protocol	Scheduled Study Day	Analysis Windows
Global/Japan	Day 1	≤1
Global/Japan	Day 31	2 - 91
Global/Japan	Day 151	92 - 255
Global/Japan	Day 361	≥ 256

Appendix 3 Analysis Window for Clinical Lab Data

Protocol	Scheduled Study Day	Analysis Windows
Japan	Day 1	≤ 1
Japan	Day 8	2 - 20
Japan	Day 31	21 - 91
Japan	Day 151	≥ 92

Appendix 4 Inclusion Criterion 2

2. The subject must meet at least 1 of the following conditions at the time of informed consent.
   (a) Diagnosed with combined immunodeficiency (severe combined immunodeficiency, X-linked hyper-immunoglobulin M [IgM] syndrome, etc); antibody deficiency (X-linked agammaglobulinemia, common variable immunodeficiency, non-X-linked hyper-IgM syndromes, etc); or other immunodeficiency (Wiskott-Aldrich syndrome, DiGeorge syndrome, etc), or
   (b) Diagnosed with human immunodeficiency virus infection, or
   (c) History of organ or bone marrow transplantation, or
   (d) Subject is receiving immunosuppressive chemotherapy, or
   (e) Subject is receiving systemic high-dose corticosteroid therapy (prednisone equivalents $\geq$ 0.5 mg/kg every other day, other than inhaler or topical use), or
   (f) Subject is receiving other immunosuppressive therapy (eg, azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, cytokine inhibitors, etc)

   All efforts will be made to recruit subjects for representation across all the immunocompromised conditions indicated in inclusion criteria (a) - (f).

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Document Title:	Statistical Analysis Plan Edition 3	
Document ID:	CCI [redacted]	
Version Label:	4.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
21-Nov-2022 07:58 UTC	PPD	Content Approval
21-Nov-2022 07:13 UTC	PPD	Qualified Person Approval

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